Novel and Unexpected Deamination during the Palladium-Catalysed Cross-Coupling of Haloanilines and Arylboronic Acids

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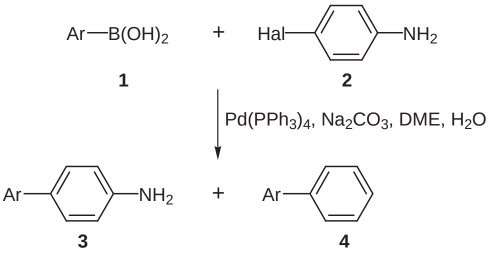
Abstract: Palladium-catalysed cross-coupling reactions involving haloanilines and arylboronic acids produce the expected biaryl products, but additionally a substantial quantity of the corresponding deaminated biaryl is also generated which constitutes a novel synthetic methodology.

Key words: deamination, palladium-catalysed, cross-coupling, arylboronic acids

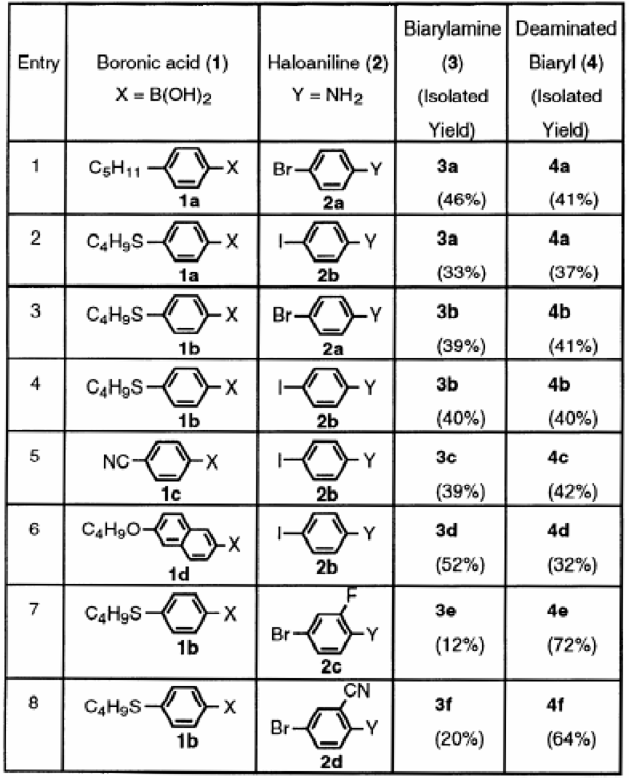
Palladium-catalysed cross-coupling reactions are now firmly established as extremely valuable procedures in organic synthesis. [1-5] Small, easily managed sub-units with the desired substitution patterns can be prepared and then coupled together using high-yielding cross-coupling methods in a convergent synthetic strategy. The potential use of the sub-units in a variety of different coupling reactions enables many compounds to be prepared in a systematic, economic and efficient manner. Many types of palladium-catalysed cross-coupling reactions have been reported, mostly involving zinc, [6] tin[7,8] and boron[1,2,5] organometallic units coupling to units with chloro, bromo, iodo and triflate leaving group, but those involving boronic acid organometallics have many advantages and are particularly popular. [9]

Recently, we have been using palladium-catalysed cross-coupling reactions (Scheme 1 and Table 1) of arylboronic acids (**1**) with haloanilines (**2**) in the attempted efficient preparation of several aminobiaryls (**3**) as intermediates for the synthesis of some isothiocyanato-substituted biaryls for use in third-order non-linear optical applications. However, during such reactions, deamination occurred unexpectedly to give substantial yields of deaminated biaryls (**4**). This result is particularly surprising because palladium-catalysed cross-coupling reactions involving boronic acids are widely reported to have an excellent tolerance towards many functional groups and such couplings involving haloanilines have been reported previously, [3,4] without any indication that deamination occurs. In fact many papers describe the efficient synthesis of *N*-aryl tertiary amines through the palladium-catalysed cross-coupling of a secondary amine with an aryl bromide. [10-13] More recently, the cross-coupling of arylboronic acids at the hydrogen site of amines to generate *N*-substituted aryl amines, again without the occurrence of deamination, has been reported. [14]



Scheme 1

Table 1. Palladium-catalysed cross-coupling of a range of arylboronic acids and haloanilines and concomitant deamination.



Entry	Boronic acid (**1**) X = $B(OH)_2$	Haloaniline (**2**) Y = NH_2	Biarylamine (**3**) (Isolated Yield)	Deaminated Biaryl (**4**) (Isolated Yield)
1	C_5H_{11} X **1a**	Br Y **2a**	**3a** (46%)	**4a** (41%)
2	C_4H_9S X **1a**	I Y **2b**	**3a** (33%)	**4a** (37%)
3	C_4H_9S X **1b**	Br Y **2a**	**3b** (39%)	**4b** (41%)
4	C_4H_9S X **1b**	I Y **2b**	**3b** (40%)	**4b** (40%)
5	NC X **1c**	I Y **2b**	**3c** (39%)	**4c** (42%)
6	C_4H_9O X **1d**	I Y **2b**	**3d** (52%)	**4d** (32%)
7	C_4H_9S X **1b**	F Br Y **2c**	**3e** (12%)	**4e** (72%)
8	C_4H_9S X **1b**	CN Br Y **2d**	**3f** (20%)	**4f** (64%)

All products (**3a-f** and **4a-f**) were found to be >99.5% pure by HPLC analysis and gave satisfactory NMR, IR, MS and CHN data.

During the coupling of arylboronic acid **1a** with 4-bromoaniline (**2a**) using the typical reaction conditions (see Scheme 1 and Table 1) the starting bromide (**2a**) was consumed within 1 hour, but surprisingly GLC analysis revealed the presence of two products in a 1:1 ratio (entry 1, Table 1). Analysis by GC-MS indicated the material of longer retention time to be the desired amine product (**3a**) and the other product to be the deaminated analogue (**4a**). Compounds **3a** and **4a** were easily isolated (46% and 41% yields respectively) by column chromatography, and spectroscopic and elemental analyses confirmed the structures.

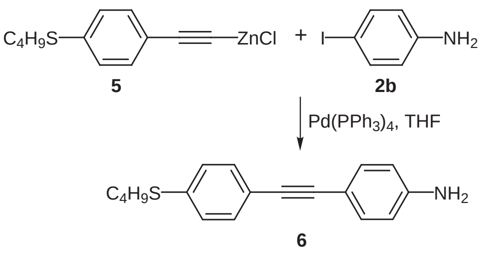
Further investigations through the careful monitoring of a repeat of entry 1 (Table 1) by GLC analysis did not reveal the presence of any bromobenzene throughout the reaction and failed to detect any deamination after the coupling reaction was complete. These results suggest that the deamination process occurs simultaneously with the coupling reaction, or perhaps simply requires the presence of the arylboronic acid.

The coupling reaction was carried out using 4-iodoaniline (**2b**) (entry 2, Table 1) in an attempt to reduce deamination by increasing the rate of coupling. However, continuous GLC analysis revealed similar results to those obtained for entry 1 with a similar ratio (1:1) of compound **3a** to compound **4a**, although isolated yields are slightly different (Table 1).

Further combinations of arylboronic acids and haloanilines in palladium-catalysed cross-coupling reactions have all resulted in substantial amounts of a deaminated biaryl product. Entries 3 and 4 (Table 1) are analogous to entries 1 and 2 respectively, but employed an alkylsulfanyl-substituted boronic acid (**1b**). However, the results of the coupling reactions are identical with a 1:1 ratio (GLC analysis) of the desired aminobiaryl (**3b**) and the deaminated biaryl (**4b**) recorded, and yields of around 40% of each were isolated. Similarly, when the cyano-substituted boronic acid (**1c**) was used (entry 5) isolated yields were 39% and 42% for the aminobiaryl (**3c**) and the deaminated biaryl (**4c**) respectively. The use of the naphthylboronic acid (**1d**) did generate a higher proportion of the desired aminobiaryl (**3d**) (52%), but a 32% yield of the deaminated biaryl (**4d**) was also isolated. These results (entries 1-6) show that the nature of the boronic acid does not seem to affect significantly the outcome of the coupling reaction and deamination.

Different anilines (**2c** and **2d**), each with an electron-withdrawing substituent *ortho* to the amine group, were also used (entries 7 and 8). When 4-bromo-2-fluoroaniline (**2c**) was used in a palladium-catalysed cross-coupling reaction with boronic acid **1b**, the desired aminobiaryl (**3e**) was obtained in just 12% yield, and a 72% yield of the deaminated biaryl (**4e**) was isolated. It is probable that the electron-withdrawing effect of the *ortho* fluoro substituent is responsible for the enhanced degree of deamination, a view supported by the result shown in entry 8 for the coupling of 2-amino-5-bromobenzonitrile (**2d**) with boronic acid **1b**. In the case of entry 8, the degree of deamination is not as significant as seen for entry 7, but 64% of the deaminated biaryl (**4f**) was isolated in comparison to only 20% of the desired aminobiaryl (**3f**).

In four cases, it is possible that the deaminated products **4a-d** (entries 1-6) could have resulted from the coupling of the phenyl from triphenylphosphine with the arylboronic acid, as reported by Novak and co-workers.[15] However, the deaminated products **4e-f** (entries 7 and 8) retain the lateral substituent from the starting amine and could not possibly have arisen from this route.



Scheme 2

Control experiments were carried out in which amines that are incapable of coupling (4-pentylaniline and 4-chloroaniline) and 4-methoxyphenylboronic acid were subject separately to the usual reaction conditions described for entry 1, Table 1. In each case, no deamination was detected by GLC analysis, which appears to support our original evidence that the deamination occurs simultaneously with the coupling.

It is also interesting that of the organometallic units (zinc and tin) that we have used in palladium-catalysed cross-coupling reactions,[5] only those involving the boronic acid species cause deamination. For example, the coupling of the phenylethynylzinc chloride (**5**) to 4-iodoaniline (**2b**) gave a good isolated yield (67%) of amine **6** without any deamination (Scheme 2).

Deamination is a relatively difficult process to achieve, yet it has been shown to occur under the relatively mild conditions of palladium-catalysed cross-coupling reactions employing a range of arylboronic acids and haloanilines. So far, deamination has not been achieved without concomitant coupling, and although such deamination is novel, interesting and provides additional background knowledge, the scope of the reaction is somewhat limited. Additionally, at this stage, it is impossible to suggest a mechanism for this unusual deamination. However, investigations are continuing in order to find a suitable reaction system that will generate 'deaminated starting materials' rather than 'deaminated products', which would be of considerable synthetic application and complementary to alternative procedures based on diazotisation methods.[16-18]

Typical Experimental Procedure (Entry 1)

A solution of compound **1a** (5.30 g, 0.028 mol) in DME (30 ml) was added dropwise to a stirred mixture of compound **2a** (3.90 g, 0.023 mol), sodium carbonate (4.00 g) and tetrakis(triphenylphosphine)palladium(0) (0.80 g, 0.7 mmol) in DME (30 ml) and water (40 ml). The stirred mixture was heated under reflux for 30 min. (GLC analysis revealed a complete reaction and the presence of two products in a 1:1 ratio), cooled, and water (100 ml) and ether (100 ml) were added. The aqueous layer was washed with ether (100 ml) and the combined ethereal extracts were washed with brine (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude product was purified by column chromatography [silica gel - petroleum fraction (bp 40-60 °C) with the gradual introduction of dichloromethane] to give a colourless oil (**4a**, 2.11 g, 41%, mp 9-10 °C) followed by a colourless solid (**3a**, 2.53 g, 46%, mp 71-72 °C).

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